National Institute for Health and Care Excellence

IP 1116 – Transcutaneous stimulation of the cervical branch of the vagus nerve for cluster headache and migraine
Consultation Comments table

IPAC date: 15th January 2016

Com. no.	Consultee name and organisation	Sec. no.	Comments	Response Please respond to all comments
1	Consultee 1 Specialist Adviser		Dear Sirs Many thanks for your invitation to comment – Regarding your outline this contains a number of factual inaccuracies which I feel necessary to highlight – please see below Regards	Thank you for your comment.
2	Consultee 1 Specialist Adviser	**2.1**	Cluster headaches are characterised by episodes of typical extremely severe unilateral periorbital pain, conjunctival injection, lacrimation and rhinorrhoea.	Thank you for your comment. The committee considered adding 'typical extremely severe' to the disease description but decided not to change the guidance

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3	Consultee 1 Specialist Adviser	**2.1**	Attacks can last from a few minutes to several hours and can occur many times a day, over several days (weeks, months or years).	Thank you for your comment. Section 2.1 of the guidance has been changed as follows: '' Cluster headaches are characterised by episodes of unilateral periorbital pain, conjunctival injection, lacrimation and rhinorrhoea. Attacks can last from a few minutes to several hours and can occur many times a day, *for several days, weeks, months or years*. Migraines are severe headaches *which may last for hours, days or longer,* often accompanied by nausea, photophobia, phonophobia *and the perception of unpleasant odours*. In some people migraines may be accompanied by *an* aura, characterised by the *focal neurological symptoms that usually precede or sometimes accompany the headache. The International Headache Society's International Classification of Headache Disorders classifies migraine types.*''

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4	Consultee 1 Specialist Adviser	**2.1**	Migraines are severe headaches, often accompanied by nausea, photophobia and phonophobia. In some people, migraines may be accompanied by aura which is characterised by the perception of flashing lights, the perception of unpleasant odours(the perception of unpleasant odour is not considered an aura manifestation but one of stimulus sensitivity, similar to increased sensitivity to noise or light), confusion or difficulty speaking. The usual treatment option for patients with cluster headache or migraine is medical therapy, either to prevent or stop acute attacks. Medical treatments for acute cluster headache attacks include oxygen inhalation and medications such as triptans.	Thank you for your comment. Section 2.1 of the guidance has been changed. Please refer to response to comment 3.
5	Consultee 1 Specialist Adviser	**2.2**	Corticosteroids and verapamil may be used to prevent or reduce the frequency of cluster headaches. Medical treatments for acute migraine attacks include analgesics, triptans and anti-emetics. Beta-blockers, tricyclic antibiotics (you mean tricyclic antidepressants not antibiotics),	Thank you for your comment. Section 2.2 of the guidance has been changed as follows: '' The usual treatment option for patients with cluster headache or migraine is medical therapy, either to *stop or prevent* attacks. Treatments for acute cluster headache attacks include oxygen inhalation and medications such as triptans. Corticosteroids and verapamil may be used to prevent or reduce the frequency of cluster headaches. Treatments for acute migraine attacks include analgesics, triptans and anti-emetics *(as recommended in NICE's guideline on headaches in over 12s)*. Beta-blockers, tricyclic *antidepressants and antiepileptics (topiramate, sodium valproate)* may be used to prevent or reduce the frequency of migraine attacks.''

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6	Consultee 1 Specialist Adviser	**2.2**	pizotifen (pizotifen is not a recommended treatment for migraine according to existing NICE guidance CG150) and anticonvulsants may be used to prevent or reduce the frequency of migraine attacks.	Thank you for your comment. Section 2.2 of the guidance has been changed. Please refer to response to comment 5.
7	Consultee 1 Specialist Adviser	**2.3**	Surgical treatments are reserved for patients with distressing symptoms that are refractory to medical treatments. For patients with chronic cluster headache, surgical treatments include deep brain stimulation to modulate central processing of pain signals, and radiofrequency ablation to interrupt trigeminal sensory or autonomic pathways (I am not aware of any major headache specialists or units in the UK using RF ablation procedures to interrupt trigeminal or autonomic pathways, yet some units suggest treatment with trigeminal nerve stimulation (Cefaly) or single pulse transcranial magnetic stimulation (eNeura) and obviously.	Thank you for your comment. Section 2.3 of the guidance has been changed as follows: '' *Invasive* treatments are reserved for patients with distressing symptoms that are refractory to medical treatments. For patients with chronic cluster headache, *these* include deep brain stimulation to modulate central processing of pain signals. For patients with chronic migraine, *these* include *treatments such as nerve blocks, botulinum toxin (see NICE's technology appraisal guidance on botulinum toxin type A for the prevention of headaches in adults with chronic migraine), acupuncture or nerve stimulation.* '' Please also refer to comment 48.
8	Consultee 1 Specialist Adviser	**2.3**	For patients with chronic migraine, surgical (I would classify occipital nerve blocks as invasive procedures but not a surgical treatment as such – some patients are also treated with multiple cranial nerve blocks)treatments include occipital nerve blocks and occipital nerve stimulation.	Thank you for your comment. Section 2.3 of the guidance has been changed. Please refer to response to comment 7.

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9	Consultee 1 Specialist Adviser	**2.2**	You have missed out one of the major advances in the treatment of migraine for which there is NICE guidance, namely cranial botulinum toxin injections.	Thank you for your comment. Section 2.3 of the guidance has been changed. Please refer to response to comment 7.
10	Consultee 1 Specialist Adviser	**2.1**	Migraines are headaches which may last hours, days or longer.	Thank you for your comment. Section 2.1 of the guidance has been changed. Please refer to response to comment 3.
11	Consultee 1 Specialist Adviser	**2.1**	re introduction re cluster headache: ...can occur many times a day, over several weeks or months, or years	Thank you for your comment. Section 2.1 of the guidance has been changed. Please refer to response to comment 3.
12	Consultee 1 Specialist Adviser	**NOTE**	I am / have been [redacted] for studies of Gammacore in the UK and I have received financial contributions and reimbursement to attend conferences and act as a clinical and scientific advisor to the company.	Thank you for your comment.
13	Consultee 1 Specialist Adviser	**2.2**	Section 2.1 should say - tricyclic antidepressants not antibiotics ? should include pizotifen, a drug not recommended within NICE guidelines and one rarely used by headache specialists these drugs may reduce the frequency or severity of attacks.	Thank you for your comment. Section 2.2 of the guidance has been changed. Please refer to response to comment 5.
14	Consultee 1 Specialist Adviser	**2.3**	Section 2.3 I am not aware of any experts in subspecialty headache (as opposed to pain consultants who do not generally regard themselves as headache experts) using RF ablation procedures as typical therapy and I am not aware of such procedures being used in conventional specialist units. In addition,	Thank you for your comment. Section 2.3 of the guidance has been changed. Please refer to response to comment 7.

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15	Consultee 1 Specialist Adviser	**3.2**	Section 3.2 stimulation is increased until there is a pulling down of the lip on that side - muscle contractions under the skin may occur but do not indicate the position is either in the correct position or at maximal amplitude, it is the lip pull that demonstrates this. I have some caution in advising this, as further trials require a patient to be ignorant of this fact - placebo devices may cause contraction of muscles and yet appropriate vagal nerve stimulation and lip pull are not seen. We do not wish to cause future potential blinding problems for ongoing studies	Thank you for your comment. The description in section 3.2 of the guidance matches the Instructions For Use from the manufacturer of the device. The committee decided not to change the guidance.
16	Consultee 1 Specialist Adviser	**5.1**	Section 5.1 I have extensive use of Gammacore VNS in the PREVA and acute attack cluster headache study and also in a large number of patients in clinical practice. I have not come across any worrying or adverse side effects likely to be due to the device. This has been, in these patients, safe and quite often highly effective, including in many patients refractory to other existing treatments. Theoretical adverse effects are also unlikely duie to the low voltage of the device and its apparent inability to stimulate efferent vagal nerves	Thank you for your comment. The safety outcomes reported are those which are described in the available evidence.

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17	Consultee 4 NHS Professional	**General**	This is a useful option to the management of migraine and particular cluster headache. The current pricing of the device is directed at situations where existing interventions have failed but if this was more appropriately priced I think it could be a useful first line management in a clinical area where patients do not like taking regular medication. As a GP with a special interest in headache I run intermediate care headache clinic and have had success in about 50% of patients in whom it has been used and no feedback of any side effects. There is an emerging evidence base which is supportive. I have no personal conflicts of interest or have received any pecuniary benefits from this company.	Thank you for your comment and for sharing your experience of this procedure. Cost-effectiveness is not part of the remit of the IP Programme. The Interventional Procedures programme at NICE assesses the safety and efficacy of new interventional procedures. The committee makes recommendations on conditions for the safe use of a procedure including training standards, consent, audit and clinical governance. It does not have a remit to determine the placement of a procedure in the pathway of care for a disease or condition.
18	Consultee 5 NHS Professional	**General**	I have several patients with cluster headache who have tried the nVNS device. I have seen improvment especially in one gentleman who had not responded to traditional treatments. This gentleman had tried high dose Verapamil with no effect, high dose Topiramate with no effect and Lithium with moderate results. He was using 2 sumatriptan injections per day as well as additional sumatriptan tablets to get through the night. Since using nVNS he has removed all his other medications and is managing on occasional sumatriptan injections and oxygen. This has made significant improvment to this gentleman and is now back to work full time.	Thank you for your comment and for sharing your experience of this procedure.

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19	Consultee 6 electroCore LLC	**General**	Dear Professor Campbell: Please find a letter from [redacted] and I outlining a series of questions we have regarding the recent IPAC guidance rendered for Transcutaneous Stimulation of the Vagus Nerve. I believe the letter is self explanatory but ultimately we hope to get a few minutes of your time to better understand some of the points outlined in the guidance. Happy Holidays,	Thank you for your comment.
20	Consultee 6 electroCore LLC	**General**	Dear Professor Campbell, ElectroCore is aware of, and has reviewed the draft guidance from IPAC relating to transcutaneous stimulation of the vagus nerve (tVNS, or our preferred "nVNS" for non-invasive vagus nerve stimulation) for cluster headache and migraine. It is our intention to respond fully, in the appropriate way, to this draft guidance during the current consultation period. I was wondering, however, if it might be possible to have a short telephone conversation with you to discuss a couple of areas of concern that we have regarding the current draft, and to gain your advice as to the most appropriate way to proceed.	Thank you for your comment.

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21	Consultee 6 electroCore LLC	**1**	We were surprised to see that the positive recommendation for use of tVNS was qualified by a requirement that the treatment should only be provided where "arrangements are in place for clinical governance, consent and audit or research". Given that there are no safety issues around this procedure, this recommendation strikes us as unnecessary. Such a recommendation, would surely be more usual in circumstances where it is necessary to inform patients of significant risks, so that they are able to balance potential safety considerations against the likely outcome of success from the intervention. But that is not the case here.	Thank you for your comment. Section 1.1 of the guidance states that ‘’Current evidence on the safety of transcutaneous stimulation of the cervical branch of the vagus nerve for cluster headache and migraine raises no major concerns. The evidence on efficacy is limited in quantity and quality. Therefore, this procedure should only be used with special arrangements for clinical governance, consent and audit or research.’’ The committee considered this comment but decided not to change the main recommendations.

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22	Consultee 6 electroCore LLC	**6.1**	Second, we note that cluster headache is described as very common, and the draft guidance goes on to suggest that the evidence for the use of tVNS in that condition as lacking. Neither of these points is correct. While migraine is a relative common condition, cluster headache is quite significantly uncommon (having a reported prevalence of less than one in a thousand). As a result, and given that the study data relating to the use of tVNS is quite large compared to any other studies that have been conducted in the field, we respectfully disagree with any conclusion that these data are lacking. Furthermore, the studies were also conducted to the highest standards, by the most well respected neurologists and headache specialists in the world.	Thank you for your comment. Section 6.1 of the guidance has been changed and sections 6.2 and 6.3 have been added as follows: ‘’ 6.1 The Committee noted that *migraine is a very common condition* and therefore good evidence of efficacy is particularly important. This consideration contributed to the recommendation for further research. *6.2 The Committee noted that cluster headache is a rare condition and that few effective treatment options exist for it.* *6.3 The Committee noted that the evidence for the efficacy of transcutaneous stimulation of the cervical branch of the vagus nerve for cluster headache was better than for migraine.’’*

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23	Consultee 6 electroCore LLC	**General**	These curious aspects of the draft guidance leave us to question whether these findings of the IPAC are being driven mainly by cost efficacy concerns. Assuming that is indeed the case, I would be very glad to discuss with you what opportunity there is for tVNS to undergo a MedTEP review in the coming months, as that is our strong intention. It is our understanding that the IPAC review and MedTEP reviews have wholly separate remits, and as such, perhaps concerns regarding cost efficacy should be reserved for the latter process. This would perhaps provide a more appropriate venue through which to demonstrate the strong evidence already gathered in support of our therapy's use in both cluster headache and migraine (by both neurologists and general practitioners), but not gathered as part of this IPAC review. More particularly, in addition to the already strong evidence for tVNS in cluster headache, we expect shortly to provide additional evidence for the intervention in migraine. We expect this to be of a quality and quantity that would qualify it for consideration in any MedTEP appraisal process.	Thank you for your comment. Cost-effectiveness is not part of the remit of the IP Programme. MTEP does consider cost implications for specific devices. The lack of evidence on efficacy underpinned the recommendation for special arrangements and further research. Procedures with 'special arrangements' recommendation may be reassessed when relevant new research is published. IPAC is pleased to hear that further research is ongoing and acknowledged this in section 6.5 of the guidance as follows: '' *The Committee noted that further evidence is likely to become available from a number of current trials*.''
24	Consultee 6 electroCore LLC	**General**	Finally, I should also like to understand better whether, assuming that tVNS emerges positively from such a review, MedTEP guidance would supersede that of IPAC?	Thank you for your comment. IPAC and MTEP have separate remits. IPAC assesses the safety and efficacy of new interventional procedures and MTEP evaluates the cost effectiveness of new or innovative medical technologies.

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25	Consultee 6 electroCore LLC	**General**	I should be most grateful if you were able to spare a few minutes to discuss with me how a MedTEP review can work alongside the IPAC process, as the latter nears completion, and to discuss these matters in greater detail. Yours sincerely,	Thank you for your comment.
26	Consultee 6 electroCore LLC	**General**	Dear Professor Campbell, RE: Transcutaneous stimulation of the cervical branch of the vagus nerve for cluster headache and migraine: Interventional procedure consultation ElectroCore is very disappointed that the IPAC has produced a draft recommendation for tVNS to be used only where special arrangements are in place for clinical governance, consent and audit or research. Since the IPAC has reached a view that tVNS is safe, we believe it should logically follow that special arrangements are not required and tVNS should be recommended for use with normal arrangements in place.	Thank you for your comment. The committee considered this comment but decided not to change the main recommendations.
27	Consultee 6 electroCore LLC	**General**	First, ElectroCore would like to draw particular attention to the fact that there are very few licensed acute treatment options for cluster headache and no approved prophylactic treatments options. To date, there are only two approved treatments for acute cluster headache, both of which have significant side effects and require close physician monitoring.	Thank you for your comment. The IP programme does not assess the efficacy and safety of comparator interventions.

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28	Consultee 6 electroCore LLC	**1.1**	Secondly, cluster headache is one of the most painful medical conditions known to man. Because of the level of discomfort, patients and physicians widely use a variety of off-label treatments, which also have significant side effects and limitations. Additionally, few options have been tested rigorously in clinical trials, and the most frequently used treatments have significant side-effects. Among those treatments tested certainly none have been done so with the level of rigor and quality of tVNS, and there is a clear need for effective treatments such as tVNS. gammaCore has been developed to address this unmet medical need for a safe, effective, and easily-administered treatment for cluster headache. We believe this clinical need, coupled with the evidence for tVNS in cluster headache, should persuade the IPAC to recommend tVNS with normal arrangements for governance, consent and audit.	Thank you for your comment. The committee considered this comment and decided to reflect this in section 6.2 of the guidance as follows: ''*The Committee noted that cluster headache is a rare condition and that few effective treatment options exist for it.*''
29	Consultee 6 electroCore LLC	**1.1**	In our view, uncertainties with regard to the clinical effectiveness of tNVS (with gammaCore) and how these may vary from patient to patient can be managed entirely adequately by the treating physician, taking into account a variety of factors including whether or not a patient is responding to treatment. Since there are no major concerns with regard to safety, we believe there is no clear justification for special measures. The Committee's current recommendations therefore appear unreasonable.	Thank you for your comment. The committee considered this comment but decided not to change the main recommendations.
30	Consultee 6 electroCore LLC	**General**	ElectroCore would like to make a number of specific comments with regard to the IPAC's draft recommendations and the rationale set out in the consultation document and these are set out below.	Thank you for your comment.

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31	Consultee 6 electroCore LLC	**1.1**	IP1116 Consultation Document Section 1.1: The safety of tVNS for cluster headache and migraine In section 1.1 of the Consultation Document the IPAC makes the following statement: “Current evidence on the safety of transcutaneous stimulation of the cervical branch of the vagus nerve for cluster headache and migraine raises no major concerns” ElectroCore is encouraged by the Committee’s acknowledgement that tVNS (with gammaCore) is a safe procedure and that the evidence available on the use of tVNS in clinical trials for cluster headache and for migraine raises no major concerns with regard to safety. We are pleased that the Committee has reached this view and note that the safety profile of tVNS represents a major breakthrough in the field of vagus nerve stimulation, which has previously required surgical intervention carrying many risks not associated with tVNS, as it is entirely non-invasive. In addition, the clinical side-effects reported for implanted VNS – including cough, pain at the stimulation site or the mandible, dysphonia and possible cardiac side-effects – have not been observed with significant frequency (or at all) in the clinical studies and/or commercial experiences with tVNS.	Thank you for your comment.

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32	Consultee 6 electroCore LLC	**1.1**	IP1116 Consultation Document Section 1.1; The Efficacy of tVNS In section 1.1 of the consultation document the following is stated: “The evidence on efficacy is limited in quantity and quality. Therefore, this procedure should only be used with special arrangements for clinical governance, consent and audit or research.” We strongly disagree with this statement. It should be noted that the clinical evidence included in NICE’s overview for chronic cluster headache represents a very significant body of evidence in the context of a condition that is poorly understood, regularly misdiagnosed and relatively rare in comparison to other primary headache conditions. Chronic cluster headache is considered by conventional standards an orphan disease. Representing less than 10% of the total cluster headache incidence, which is itself less than 10% of the migraine. Chronic cluster headache is likely to affect less than 0.1% of the population. For this reason, no pharmacological therapies have been specifically developed for chronic cluster headache and those used are supported primarily by open label studies enrolling less than 50 subjects. In contrast, the PREVA study to support the use of prophylactic tVNS, was one of the largest RCTs conducted in the chronic population.	Thank you for your comment. Special arrangements recommendation is not intended to restrict the use of a procedure. It states that clinicians using the procedure must inform the clinical governance lead in their trust, tell the patient about any uncertainties regarding the procedure and collect further data on outcomes by means of audit or research. The committee considered this comment but decided not to change the main recommendations. Sections 6.2 and 6.3 of the guidance have been changed as follows: ‘’6.2 *The Committee noted that cluster headache is a rare condition and that few effective treatment options exist for it*. 6.3 *The Committee noted that the evidence for the efficacy of transcutaneous stimulation of the cervical branch of the vagus nerve for cluster headache was better than for migraine.*’’

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33	Consultee 6 electroCore LLC	**1.1**	With regard to the IPAC's comment on "quantity and quality" of evidence on efficacy, we also note that another recent review by the IPAC led to an apparently conflicting view. In IPG527 the Committee reached the view that an RCT of 32 patients with 2 months of follow up was sufficient to support its conclusion evidence on efficacy was adequate. ElectroCore is unable to reconcile this approach with the IPACs summary statement on the current topic where an altogether more substantial body of evidence has been presented to the Committee and yet the IPAC has taken a view that efficacy data is limited in both quantity and quality. As previously mentioned, the clinical programme conducted by ElectroCore for tVNS in cluster headache, including PREVA (which studied the use of tVNS in chronic cluster headache), is the broadest, most comprehensive, and largest study group reported in this field. The quality of the clinicians who participated in this work is beyond question, as many are the undisputed thought leaders in the headache neurology field.	Thank you for your comment. Section 1.1 of IPG 527 (Implantation of a sphenopalatine ganglion stimulation device for chronic cluster headache) sates: 'Current evidence on the efficacy of implantation of a sphenopalatine ganglion stimulation device for chronic cluster headache, in the short term (up to 2 months), is adequate. With regard to safety, a variety of complications have been documented, most of which occur early and resolve; surgical revision of the implanted system is sometimes needed. Therefore, this procedure should only be used with special arrangements for clinical governance, consent and audit or research.' The evidence was based on 43 patients from 2 randomised controlled trials and 1 case series. For IP 1116, the overview was based on 214 patients from 1 randomised controlled trial and 4 case series. The Committee considered this comment but decided not to change the main recommendations.

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34	Consultee 6 electroCore LLC	**6.1**	IP1116 Consultation Document Section 6.1; The epidemiology of primary headache conditions In section 6.1 of the draft guidance, the Committee states: "The Committee noted that cluster headache and migraine are very common conditions and therefore good evidence of efficacy is particularly important. This consideration contributed to the recommendation for further research." ElectroCore is alarmed by this statement which appears to suggest that the IPAC is not familiar with the epidemiology of cluster headache. To describe cluster headache as a very common condition is at odds with the entire literature and current scientific understanding of a condition with a 1-year prevalence estimated at 5 per 10,000 (Fischera, 2008).	Thank you for your comment. Section 6.1 of the guidance has been changed and section 6.2 has been added. Please refer to response to comment 22.
35		**6.1**	Presumably, given cluster headache is in fact consistently regarded as a very rare primary headache condition, the IPAC's related conclusion in 6.1 ("therefore good evidence of efficacy is particularly important") must be re-evaluated. As a rare condition, high enrolment in a study is a practical impossibility. It is, of course, the statistical significance of the study results that should be the driving force behind a conclusion regarding the quality of the evidence (along with the clinicians providing of the data previously discussed). The PREVA data reveal statistical and clinical significance across all endpoints.	Thank you for your comment. Section 6.3 of the guidance has been changed as follows: ''*The Committee noted that the evidence for the efficacy of transcutaneous stimulation of the cervical branch of the vagus nerve for cluster headache was better than for migraine.''*

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36	Consultee 6 electroCore LLC	**6.2**	IP1116 Consultation Document Section 6.2 Placebo Effects In section 6.2 of the consultation document the Committee states: “In its interpretation of the evidence, the Committee noted the potential for a placebo response and the relapsing and remitting course of cluster headaches and migraine.” The Committee statement that cluster headache has a relapsing and remitting course is over-simplistic and misleading. NICE would be correct to note that migraine as well as certain cluster headache groups may have a relapsing and remitting course – in particular this would apply to episodic cluster headache. However, chronic cluster headache (i.e. the focus of the evidence base for tVNS as reported in the PREVA study) does not have a relapsing and remitting course by its very definition (ICHD-3). In order for a diagnosis of chronic cluster headache to be confirmed, symptoms must persist for over a year with no remission lasting more than one month. All patients in the PREVA study has a multi-year history of chronic cluster headache without remission and were considered refractory to multiple forms of treatment by the most accomplished tertiary care headache centres in the UK and EU. ElectroCore would encourage the Committee to reconsider its position on the evidence base for tVNS – particularly in relation to the PREVA study and with respect to the substantial and clinically meaningful benefits observed in patients with chronic cluster headache.	Thank you for your comment. The committee considered this comment but decided not to change the main recommendations. The committee has revised its committee comments in section 6.

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37	Consultee 6 electroCore LLC	**1.2**	IP1116 Consultation Document Section 1.2; Guidance for treating clinician In section 1.2 of the consultation document the following guidance is provided for treating clinician: “Ensure that patients understand the uncertainty about the procedure’s efficacy and provide them with clear written information.” We note that this is a standard form of advice to the NHS from the IPAC. However, we are concerned that the draft guidance provides no detailed rationale with regard to the drivers of this uncertainty and it is therefore hard to envisage how these matters could be communicated in a helpful way to patients. Unless a clinician was informing the patient about this so that they could balance any risks associated with treatment against the possible benefit, it is unclear why this warning would be any more necessary for tVNS than any more of the thousands of other treatments or interventions that work better in some patients than others and around which there is uncertainty relating to efficacy. Given that there are no safety issues relating to tVNS, we are not clear why this warning is necessary.	Thank you for your comment. The committee considered this comment but decided not to change the main recommendations. The lack of evidence on efficacy underpinned the recommendation for special arrangements and further research.
38	Consultee 6 electroCore LLC	**5**	Section 5; Safety evidence for tVNS In section 5 a summary of safety outcomes is provided from the published literature that the Committee considered as part of the evidence about this procedure. electroCore now has a integrated safety database with > 500 patients. In this dataset > 95% of the device related AEs are considered mild, transient and resolve upon the completion of the treatment.	Thank you for your comment. The committee stated in section 1.1 of the guidance that ‘‘Current evidence on the safety of transcutaneous stimulation of the cervical branch of the vagus nerve for cluster headache and migraine raises no major concerns.’’

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39	Consultee 6 electroCore LLC	**6.4**	IP1116 Consultation Document Section 6.4 Patient Commentary In section 6.4 of the consultation document the following statement appears “The Committee noted patient commentary, much of which was favourable.” ElectroCore notes that, in fact, almost all of the patient commentary was positive and the group of patients from whom views were sought wasn't inconsiderable. Beyond noting the patient commentary, it is not clear whether the Committee has made adequate attempts to take these views into account.	Thank you for your comment. The committee very much welcomes hearing from patients who have undergone this procedure and considers their experience and views in their deliberations (please refer to section 10.3 of the IP programme manual).
40	Consultee 6 electroCore LLC	**General**	In summary, ElectroCore hopes that the IPAC gives further careful consideration to the concerns raised during consultation and that the Committee’s preliminary recommendations for tVNS are amended to give access to a much needed, clinically effective and safe treatment option for patients suffering from debilitating primary headache conditions. Yours sincerely,	Thank you for your comment. The committee considered this comment but decided not to change the main recommendations.
41	Consultee 12 NHS Professional	**6.1**	I would disagree that cluster headache is a common condition. Its lifetime prevalence is around 0.5% and in 80% of cases is episodic. The effective treatment options are extremely limited and do come with considerable safety concerns.	Thank you for your comment. Section 6.1 of the guidance has been changed and sections 6.2 and 6.3 have been added. Please refer to response to comment 22.

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42	Consultee 12 NHS Professional	**1.1**	My experience of this treatment in around 40 patients has been positive with 1 patient complaining of increased cluster headache but the treatment being well tolerated. I am concerned that in this group the need for clinical governance approval is likely to lead to unnecessary delay in patients receiving treatment and that in many by the time approval would be granted their bout of cluster headache may have passed, and that more straightforward access should be considered in this group.	Thank you for your comment. The committee considered this comment but decided not to change the main recommendations. Special arrangements recommendation is not intended to restrict the use of a procedure. It states that clinicians using the procedure must inform the clinical governance lead in their trust, tell the patient about any uncertainties regarding the procedure and collect further data on outcomes by means of audit or research.
43	Consultee 13 Specialist Adviser Association of British Neurologists, Headache and Pain Advisory Group	**1.1**	"1. The Association of British Neurologists Advisory Group for Headache & Pain (ABN AAG) agrees with the NICE consultation recommendation 1.1 especially in relation to the safety of the procedure. The AAG feel it is important to point out that the safety of this intervention is a very important issue when compared to other treatments used in chronic cluster headache as the currently used standard care treatments have significant potential cardiac and toxicity issues needing frequent monitoring with associated cost i.e. ECG monitoring for Verapamil, Drug levels for Lithium etc. Thus a new, effective & safe treatment is welcomed. In addition, its low side effect profile makes it attractive as a potential primary therapy for cluster headache occurring in pregnancy or in other special patient populations, where conventional acute abortive or preventative therapies for cluster headache are contraindicated. "	Thank you for your comment. Section 6.2 has been changed as follows ‘’ *The Committee noted that cluster headache is a rare condition and that few effective treatment options exist for it.*’’

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44	Consultee 13 Specialist Adviser Association of British Neurologists, Headache and Pain Advisory Group	**1.3**	"2. The ABN AAG for Headache & Pain fully and strongly agree with NICE recommendation 1.3 outlining the need for more extensive research in relation to the utility of this intervention in migraine. There a strong consensus, based on both research data and extensive patient usage experience, that this intervention appears beneficial in the preventative treatment of cluster headache, and in some previous medically refractory patients it has avoided the need to escalate to more invasive and expensive surgical therapies for refractory chronic cluster headache."	Thank you for your comment.
45	Consultee 13 Specialist Adviser Association of British Neurologists, Headache and Pain Advisory Group	**General and 1.3**	"3. The ABN Headache & Pain AAG remain undecided about the potential role for Transcutaneous stimulation of the cervical branch of the vagus nerve in the treatment of Migraine and strongly recommend the need for further larger well-constructed trials in this area before this intervention should be widely recommended or adopted for the treatment of migraine. Based on general consensus and knowledge of unpublished data there may be a suggestion of potential benefit in chronic migraine when this procedure is used over a prolonged treatment period, but on balance we feel this hypothesis needs further research studies with sham controlled data to confirm or refute this possibility."	Thank you for your comment.
46	Consultee 13 Specialist Adviser Association of British Neurologists, Headache and Pain Advisory Group	**4 and 5**	"4. The ABN Headache & Pain AAG are aware of the currently unpublished sham controlled â€œEVENT studyâ€• of approximately 50 patients with chronic Migraine. i.e. â€œPrevention of Chronic Migraine (EVENT) Study presented at 2014 international meetings but are yet to see this appear in peer reviewed published format. [Silberstein A.D et al. Poster at the American Headache Society meeting 2014: Non-invasive Vagus Nerve Stimulation for Chronic Migraine Prevention in a Prospective, Randomized, Sham-Controlled Pilot Study (the EVENT Study); Report From the Double-blind Phase: Schoenen J, Gaul C, Silberstein S, Presented at the 4th European Headache and Migraine Trust International Congress, Copehagen, September 20, 2014.]"	Thank you for your comment. Conference presentations are not normally considered adequate to support decisions on efficacy and are not generally selected for presentation in the overview, unless they contain important safety data.

Com. no.	Consultee name and organisation	Sec. no.	Comments	Response Please respond to all comments
47	Consultee 13 Specialist Adviser Association of British Neurologists, Headache and Pain Advisory Group	**2.2**	"5. The ABN Headache & Pain AAG would like to point out to NICE that section 2.2 merits minor factual alteration in relation to treatments used for the prevention of migraine. The manufacture of pizotifen has recently been discontinued by Novartis and it may not be available in future. â€œAnticonvulsantsâ€• is too broad a term to describe migraine preventative medications as only 2 anticonvulsant drugs have supportive multiple DBRCT data to support their use in migraine prevention i.e. topiramate (See NICE Clinical Guideline CG150) and sodium valproate (see other Guidelines in UK (e.g. BASH), Europe (European Federation of Neurological Societies, EFNS) & USA (American Academy of Neurology, AAN)."	Thank you for your comment. Section 2.2 of the guidance has been changed. Please refer to response to comment 5.
48	Consultee 13 Specialist Adviser Association of British Neurologists, Headache and Pain Advisory Group	**2.3**	"6. The ABN Headache & Pain AAG would like to point out to NICE that section 2.3 also merits minor factual alteration in relation to surgical treatments used for the prevention of chronic cluster headache. It may be useful to reference the recently published NICE IPG 527 relating to neuro-modulation therapy for chronic cluster headache rather than radiofrequency ablation as the latter is now rarely if ever used in speciality headache clinical practice. "	Thank you for your comment. Section 2.3 of the guidance has been changed. Please refer to response to comment 7.
49	Consultee 15 NHS professional	**General**	Dear NICE Committee and IP Team, I am one of the physicians trying to submit my comments regarding GID-IP116 Transcutaneous stimulation of the cervical branch of the vagus nerve . I have made several attempts from my laptop and computer, last night as well as this morning. I consistently an error message (screen shot attached as well as a screen shot of part of the completed form on line, before submission fails). Below, I am including a typed form of the Specialist Questionnaire, with my answers and comments. I would be very grateful for a confirmation of receipt. With Kind regards and many thanks,	Thank you for your comment. The IP programme would like to apologise for the difficulty encountered by the consultee while trying to submit his/her comments.

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50	Consultee 15 NHS professional	**NOTE**	Specialist Questionnaire Dr [redacted] [redacted] [redacted] Hospital, England Disclosure: Since [redacted], I have a consultancy agreement with the company manufacturing the device, for financial compensation of part of my activities involving use of the device in clinical care, and offering medical advice within clinical research. I make the enclosed comments in my quality of NHS physician	Thank you for your comment and for spontaneously submitting a specialist advisor questionnaire to IPAC.
51	Consultee 15 NHS professional	**General**	Number and title of the procedure GID-IP116 Transcutaneous stimulation of the cervical branch of the vagus nerve 1. Do you have adequate knowledge on the procedure? 1.1. Does the title above describe the procedure adequately? Yes Comment : In published literature this therapy is also referred to as non-invasive vagus nerve stimulation (nVNS) to discriminate from the invasive treatment modalities, including implantable vagus nerve stimulator devices, which also target the cervical portion of the vagus nerve.	Thank you for your comment.

Com. no.	Consultee name and organisation	Sec. no.	Comments	Response Please respond to all comments
52	Consultee 15 NHS professional	**General**	2. Your involvement in the procedure 2.1 Is the procedure relevant for your speciality? 2.1 Yes Comment: As a member of a tertiary headache centre I have found tVNS to be a valuable addition to the therapeutic alternatives to offer in the last 3 years, which, with increasing number of treated patients, has proven to be safe, well tolerated, with a therapeutic potential comparable to standard of care treatments.	Thank you for your comment.

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53	Consultee 15 NHS professional	**General**	2.2.1. If you are in a speciality which does this procedure, please indicate your experience with it I perform the procedure regularly Comment: Our initial experience tVNS in a pilot cohort study on cluster headache has supported IP Committee's initial review (1). Work is in progress in collecting further observations in an increasing number of patients with migraine, cluster headache, as well as patients with primary headache conditions, complicated by medication overuse. Ref: 1. Nesbitt et al. Initial use of a novel non-invasive vagus nerve stimulator for cluster headache treatment. Neurology. 2015; Mar 24;84(12):1249-53 Using appropriate pathways after obtaining patients' consent we undertook to review the impact of tVNS on the need of medical attention and treatment. The review is analysing the impact of introducing tVNS treatment, on patients' need for medical attention, prescribed medication as well as a general health economic analysis comparing equivalent time periods before and after start of treatment with tVNS . Overall we found an improved quality of life, reduction of absence from work due to their headache condition, reduction in the number of the visits to the GP surgeries and A&E, decrease in the need for medications and considerable cost savings, after taking into consideration the cost of tVNS.	Thank you for your comment. The Nesbitt (2015) study is already included in Table 2.

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54	Consultee 15 NHS professional	**General**	2.2.2 If your speciality is involved in patient selection or referral to another speciality for this procedure, please indicate your experience with it I have taken part in patient selection or referred a patient for this procedure at least once Comment: Due to its therapeutic potential for multiple conditions involving the physiology of the vagus nerve (which is essential in regulation of most of the vital functions) a multidisciplinary collaboration to explore the potential of tVNS for the treatment of gastrointestinal disorders, asthma, chronic pain syndromes other than headache, epilepsy, anxiety as well as chronic fatigue has been in progress. Some additional comments will be made in section 4.7. I have referred patients for consideration of management of gastrointestinal disorders and sleep disturbance, with tVNS in whom we also aimed to use the procedure for treatment of their headache conditions.	Thank you for your comment.

Com. no.	Consultee name and organisation	Sec. no.	Comments	Response Please respond to all comments
55	Consultee 15 NHS professional	**General**	2.3. Please indicate your research experience relating to this procedure (please choose one or more if relevant): I have undertaken bibliographic research on this procedure I have undertaken clinical research on this procedure involving patients or healthy volunteers Comment: Our cohort pilot study published in the journal Neurology served to design conventional randomised clinical trials for tVNS for the treatment (preventive and acute) of episodic as well as chronic cluster headache. Our unpublished clinical experience with the procedure for the treatment of chronic migraine has served supporting the designing of protocols of clinical trials for the acute and preventive management of episodic as well as chronic migraine patients. I have acted as Professor [redacted] Co-investigator in the first sham-controlled clinical trial for the acute treatment of cluster headache. I have also contributed to designing this clinical trial which has included multiple sites within the UK and Europe .Data is being analysed and discussed at present.	Thank you for your comment.

Com. no.	Consultee name and organisation	Sec. no.	Comments	Response Please respond to all comments
56	Consultee 15 NHS professional	**General**	3. Status of the procedure 3.1 Which of the following best describes the procedure (choose one) The first in a new class of procedure Comment: tVNS with the gammaCore device is a novel non-invasive way of delivery stimulation to the cervical portion of the vagus nerve. From the experience I am aware of, during the last 2 years there has been a considerable increase in the extent in which the procedure has been used in clinical practice. The concept of acting directly on the nervous system for has been present in clinical practice for many years, using different therapeutic mechanisms with a development moving from implantable devices needing surgery, to non-invasive alternatives, or additional modalities, with an increasing role in primary headache syndromes' management.	Thank you for your comment.

Com. no.	Consultee name and organisation	Sec. no.	Comments	Response Please respond to all comments
57	Consultee 15 NHS professional	**2**	3.2. What would be the comparator (standard practice) to this procedure? None Comment: The procedure under review is the only device currently available for use in clinical practice, which stimulates the cervical branch of the vagus nerve, through a non-invasive route. It is the only non-invasive neurostimulation modality for which there is supportive evidence of efficacy for the acute and preventive treatment of cluster headache. For the management of migraine patients in our service tVNS, along with transcranial magnetic stimulation (SpringTMS: used with special arrangements for clinical governance) constitute invaluable, unique alternatives for treatment of episodic frequent migraine patients in whom use of acute medicines needs to be limited, and initiation of pharmacological preventive therapies is not justified. Use of non-invasive neuromodulation therapies (tVNS or TMS) has high potential in preventing the progression of episodic frequent migraine to chronic migraine and chronic migraine complicated by medication overuse.	Thank you for your comment. The committee considered this comment and decided to reflect this in section 6.2 of the guidance. Please refer to response to comment 28.
58	Consultee 15 NHS professional	**General**	3.3 Please estimate the proportion of doctors in your speciality who are performing this procedure 10% to 50% of specialists engaged in this area of work	Thank you for your comment.

Com. no.	Consultee name and organisation	Sec. no.	Comments	Response Please respond to all comments
59	Consultee 15 NHS professional	**5**	4 Safety and efficacy 4. 1 What are the adverse effects of the procedure? Please list adverse events and major risks (even if uncommon) and, if possible, estimate their incidence, as follows Adverse events reported in literature A summary of the literature additional to what was included in IP Committee's review will be provided in section 4.6 and additional information to include further safety and efficacy outcomes . No additional adverse events or side effects to what is included in IP Committee's listing were reported. Anecdotal adverse events (known from experience) In our experience, tVNS is safe and well tolerated. We have avoided use in patients with implantable medical devices. Transient discomfort at the treatment site has occurred in about 10 % of the patients. Worsening of headache, typically short lasting (about 10%) and worsening of nausea (approx. 5%) have let to treatment discontinuation with complete resolution in all patients. Transient dizziness and light-headedness in less than 10% of the patients and has typically improved with continued tVNS use. In my view this compares favourably to pharmacological alternatives.	Thank you for your comment.

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			Theoretical adverse events Clinical experience as well as data from clinical trials strongly support the increased cardiovascular safety profile in comparison to implantable vagus nerve stimulators, with growing experience with use of tVNS and no cardiovascular safety concerns. From cardiovascular view point tVNS can offer a well tolerated and safe alternative for the preventive treatment of chronic cluster headache. (2, 3). Ref. 2. Cohen AS et al. Electrocardiographic abnormalities in patients with cluster headache on verapamil therapy. Neurology. 2007 Aug 14;69(7):668-75. 3.Engel ER, et al. Non-invasive Vagus Nerve Stimulator (gammaCore) was not associated with meaningful cardiovascular adverse effects. Neurology. 2015. 84;14:suppl P1.292	
60	Consultee 15 NHS professional	**4**	4.2 What are the key outcomes for this procedure? Key efficacy of the procedure include Improvement of headache pattern: for acute treatment: termination or significant relief of the attacks within meaningful time, sustained effect and reduced need for use of alternative abortive therapy for preventive treatment: prevention of attacks or frequency reduction, lesser severity and/or duration of occurring attacks, reduced need for other therapies and Improved life quality measured by specific questionnaires (such as MIDAS, HIT-6, EQ-5D-5L)	Thank you for your comment.

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61	Consultee 15 NHS professional	**4**	4.3 Are there uncertainties or concerns about the efficacy of this procedure? If so what are they Comment: As a general experience, designing randomised, blinded, sham/placebo controlled clinical trials using devices can be more challenging than the equivalent pharmacological trials. However in my experience and view, the currently available sham devices for tNVS offer optimal blinding possibilities. This is supported by the experience that new generation sham tVNS devices have been found to have the overall estimated placebo effect for blinded interventional sham controlled studies, or slightly higher.	Thank you for your comment.
62	Consultee 15 NHS professional	**General**	4.4. What are training and facilities are required to undertake this procedure safely? The procedure is designed for safe self-admiration by the patient and does not require visits to clinics or hospital. Treatment initiation and training requires basic outpatient facilities.	Thank you for your comment.
63	Consultee 15 NHS professional	**General**	4.5 Are there any major trials or registries of this procedure currently in progress? If so please list. Yes A randomised, multicentre, double-blind, sham-controlled study of the gammaCore®-R, a non-invasive vagus nerve stimulator device for the prevention of episodic migraine- conducted in Europe and including sites in the UK A prospective, multi-centre, randomised, double-blind, sham-controlled study of the gammaCore®-S non-invasive vagus nerve stimulation device (nVNS), for the acute treatment of migraine attacks- study is being initiated and will be conducted in Italy	Thank you for your comment. IPAC is pleased to hear that further research is ongoing and acknowledged this in section 6.5 of the guidance as follows: ‘’ The Committee noted that further evidence is likely to become available from a number of current trials.’’

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64	Consultee 15 NHS professional	**5**	4.6 Are you aware of any abstracts that have been recently presented/published on this procedure that may not be listed in a standard literature search, e.g. PUBMED (this can include your own work). If yes, please list The adverse events reported in all clinical trials below were transient and mild to moderate in severity. 2 serious adverse events were reported. Both resolved and were not device related. There were no unexpected adverse events related to the study devices. Efficacy outcomes indicate high potential for therapeutic gain. 3. Silberstein S, et al. Non-invasive vagus nerve stimulation for chronic migraine prevention in a prospective, randomized, sham-controlled pilot study (the EVENT study): report from the double-blind phase Headache. 2014;54(suppl 1):1426. 4. Silberstein S, et al. Chronic migraine prevention with non-invasive vagus nerve stimulation in a prospective pilot study (the EVENT study): report from the open-label phase. Headache. 2014;54(suppl 1):1427. 5. Tepper S, Silberstein S, Mechtler L, et al. Predefined exploratory outcomes from the study of non-invasive vagus nerve stimulation for the acute treatment (ACT1) of cluster headache. Headache. 2015.	Thank you for your comment. Conference posters are not normally considered adequate to support decisions on efficacy and are not generally selected for presentation in the overview, unless they contain important safety data. The 2 Silberstein (2014) and the Tepper (2015) studies do not report any new safety events.

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65	Consultee 15 NHS professional	**General**	4.7 Is there any controversy, or important uncertainty, about any aspect of the way in which this procedure is currently being done or disseminated? No. Main dissemination pathways are national and international meetings and congresses and though patient advocacy groups. Training opportunities are available for physicians who wish to explore tVNS use in their clinical practice. Growing interest for multi-disciplinary collaboration, particularly during the past year, aiming to explore the therapeutic potential of tVNS and VNS overall, in patients with concomitant conditions, as well as furthering the understanding of the vagus nerve as a possible link between the mechanisms underlying each individual condition, has let to building of a new forum: http://vnsociety.com/posters-and-reference-articles-on-vns/ Work in progress supports the view of shared links, including changed interpretation of signals incoming to the brain from the body, resulting in an abnormal amplification, with a consequent alteration of the normal physiological reactions. This concept named Over-sensitization, is generally understood to underpin some primary headache conditions, and has become increasingly important in other disciplines such as a number of gastro-intestinal conditions and respiratory disorders.	Thank you for your comment.

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66	Consultee 15 NHS professional	**General**	5. Audit criteria Please suggest a minimum dataset of criteria by which this procedure could be audited. Safety, tolerability and clinical benefit 5.1 Outcome measures of benefit Clinical benefit including improvement in headache pattern, improved life quality measured by specific questionnaires (such as MIDAS, HIT-6, EQ-5D-5L), adherence to treatment/patient satisfaction 5.2 Adverse outcomes (including potential early and late complications) All untoward occurrences which can be of safety concern and all untoward occurrences deemed to be related/possibly related to the procedure, which do not resolve within a week after treatment discontinuation In addition, in case of choice to discontinue the treatment (by the patient or physician) should be clearly documented.	Thank you for your comment.

Com. no.	Consultee name and organisation	Sec. no.	Comments	Response Please respond to all comments
67	Consultee 15 NHS professional	**General**	Trajectory of the procedure 6.1 In your opinion, what is the likely speed of diffusion of this procedure? Relatively rapid. An increasing number of specialist physicians as well as general practitioners are becoming familiar with the procedure. Similarly, there is ongoing interest in tVNs expressed by patients. 6.2 This procedure, if safe and efficacious, is likely to be carried out in Most or all district general hospitals Comment : In addition, I anticipate use in outpatient facilities, including GP surgeries	Thank you for your comment.

Com. no.	Consultee name and organisation	Sec. no.	Comments	Response Please respond to all comments
68	Consultee 15 NHS professional	**General**	6. 3 The potential impact of this procedure on the NHS, in terms of numbers of patients eligible for treatment and use of resources, is Moderate Due to their complexity and disability, the care of primary headache conditions is in continuous need for additional safe and well tolerated alternatives. In my opinion tVNS is offers a valuable non-pharmacological, non-invasive option for management of cluster headache and migraine to ad to currently available standard of care treatments. In my experience from our headache service, and overall available evidence tNVS is safe, well tolerated and has a clear and clinically meaningful potential for efficacy, in cluster headache as well as migraine, for the chronic and episodic forms of both conditions, which can be used for both acute and preventive management. Clinical experience this far supports a therapeutic potential for tVNS for the management of primary headache disorders complicated by medication overuse. Outcomes from our review of health care utilization indicate that treatment with tVNS has good potential for cost and general resource savings with similar findings reported by Gaul et al (12), concluding a high potential for cost savings with use of tVNS. A 1 year model was used, using data from the PREVA study (included in IP Committee's review).	Thank you for your comment. Cost-effectiveness is not part of the remit of the IP Programme.

Com. no.	Consultee name and organisation	Sec. no.	Comments	Response Please respond to all comments
69	Consultee 15 NHS professional	**4 and 5**	7.1 Additional information which may be of use for NICE's review Additional publications: 6. Silberstein S, et al. Efficacy and safety outcomes of the non-invasive vagus nerve stimulation for the acute treatment (ACT1) of cluster headache study [abstract LBP07; Published online September 30, 2015]. Headache. 2015 7. Moscato D,et al. Efficacy of noninvasive vagus nerve stimulation (nVNS) in the treatment of acute migraine attacks. Headache. 2014;54(8):1418. 8.Moscato D, Moscato FR. A survey of patient perceptions of non-invasive vagus nerve stimulation (nVNS) therapy for acute migraine attacks. Cephalalgia. 2015;35(6 suppl):23. 9. Grazzi L,et al. Gammacore device for treatment of migraine attack: preliminary data. Neurology. 2014;82(10 suppl):I9-2.005. 10. Rainero I, at al. Non-invasive vagal nerve stimulation for the treatment of headache attacks in patients with chronic migraine and medication-overuse headache. Neurology. 2014;82(10 suppl):P1.262. 11. Yuan H, Silberstein S. Vagus Nerve Stimulation and Headache. Headache. 2015 Oct 16. 12. Gaul C, et al. Cost-effectiveness analysis of non-invasive vagus nerve stimulation (nVNS) for the treatment of chronic cluster headache in Germany. Cephalalgia. 2015;35(6S):81.	Thank you for your comment. Conference abstracts are not normally considered adequate to support decisions on efficacy and are not generally selected for presentation in the overview, unless they contain important safety data. The Silberstein (2015) study is an abstract that does not report any new safety event. The Moscato (2014) and (2015) studies are abstracts that do not report any new safety event. The Grazzi (2014) study is an abstract that does not report any new safety event. The Rainero (2014) study is a poster that do not report any new safety event. The Yuan (2015) paper is a review on vagus nerve stimulation. It has been included in Appendix A. The Gaul (2015) paper is poster on a cost-effectiveness analysis of nVNS. It does not report any new safety event.

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70	Consultee 15 NHS professional	**General**	Dear IP Team and NICE Committee, In addition to the emailed Specialist Questionnaire, I have compiled a summary of existing recent literature (listed in my completed Specialist Questionnaire) and included copies of abstracts and posters (and one fully published paper), which I hope the IP Committee will find of help, if possible to download for their review. With many thanks and kind regards,	Thank you for your comment and for sending us a summary of existing recent literature as well as copies of abstracts, posters and 1 published paper.
71			In clinical trials, along with an increased expectation for therapeutic benefit there is also an increased potential for reporting untoward symptoms or signs. The adverse events reported in all clinical trials included in the summary were transient and mild to moderate in severity. Two adverse events were reported: appendicitis and worsening headache. Both resolved and both of them were deemed by the investigators as not device related. There were no unexpected adverse events related to the study devices. In a double blinded, randomized, sham controlled multi-centre trial (the EVENT) study (4) Silberstein and colleagues compared the efficacy of tVNS with a sham device, for migraine prevention in chronic sufferers. A total of 30 patients were randomly assigned to receive tVNS and in a similar fashion 29 patients were distributed the sham device during a period of 2 months. The clinical investigators found that prophylactic use of tVNS in chronic migraine was associated with greater reduction of the number of headache days and improved scores in the life quality questionnaires. Prophylactic use of the tVNS for 8 weeks was associated with a reduction of 2 headache days per 28 day period. No treatment effect was seen with the sham device. 17 patients on the tVNS arm versus 16 patients in the sham group reported adverse events. The most commonly reported adverse events were general infections and not related to the study treatment.	

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72			Adverse events that were deemed as device related or possibly device related were: Facial muscle twitch was reported in 3 patients in the tVNS arm and in 1 patient in the sham group. Discomfort or swelling of the neck, face or glands were reported in 2 patients in the treatment arm and in 6 patients in the sham group. Rash or blister at the application site were reported in 2 patients in the tVNS group and in 1 patient in the sham group Worsening of migraine pain was reported in 1 patient in the tVNS group and in 2 patients in the sham group. Sore throat was reported in 1 patient in the tVNS group and 2 patients in the sham group and deemed as device related or possibly device related in the sham group. All reported adverse events were transient, mild or moderate in intensity. No serious and no unexpected adverse events were experienced. In an additional open label extension six months period of the study, (5) the benefit associated with tVNS continued to improve with time, which is consistent with the experience in clinics . In addition safety data was collected. Less than 10% (8.5%) of the patients experienced side effects that were deemed by the investigators related or possibly device related. These included blister, rash or itching at the application site in 5 patients and severe or worsening migraine pain in 3 patients. The majority of these adverse events were mild, while 1 was moderate in intensity, and all resolved. Overall, the most commonly reported adverse events were general infections and not related to the study treatment. There were two incidences of serious adverse events (appendicitis and worsening headache). Both resolved and none was deemed to be device related.	

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73			For the acute treatment of cluster headache (ACT1 study), the safety and efficacy of the tVNS was compared during a randomized, double blinded sham controlled phase of 1 month. (6). This was followed by a 3 months open label extension looking at further efficacy and safety of the use of tVNS. The study was conducted across 20 centers in the United States and included episodic as well as chronic cluster headache patients. Of a total of 150 patients 73 were randomized to use tVNS while 77 were included in the control group using the sham device. Patients treated up to 5 cluster headache attacks that occurred during the randomized phase. The response was defined as termination of attacks or a reduction in headache intensity to 1, on a 4- point severity scale (0= no pain, 4-= very severe pain) at 15 minutes after the initiation of the treatment of the first headache attack and constituted efficacy primary endpoint . Secondary efficacy endpoints were sustained treatment response, defined as response at 15minutes and 1 hour after treatment initiation, for the first treated attack and reduction in mean pain intensity of all cluster headache attacks treated during the randomized phase, comparing tVNS and sham. While there was no significant difference overall in the response rates between the tVNS (26.7%) and sham (19.2%) arms, the mean duration of the first treated attack in the randomized phase, was shorter in the population allocated the tVNS, compared to sham and the reduction in the mean duration of the first treated attack in the randomized phase compared to the last cluster headache attack before the randomized phase (at base line) was greater with tVNS than with sham. The authors conclude that although not statistically significant these differences were clinically meaningful and considered possible mechanisms behind the relatively high response to the sham treatment.	

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74			The secondary efficacy endpoints were achieved. For the patients who initiated tVNS during the open label phase the response rate was 42.4%. The primary safety endpoint was the incidence of serious adverse device effects (SADEs). Further exploration of secondary safety endpoints (incidence of adverse events and adverse device effects) revealed a safe and well tolerated profile: A total of 72 patients reported adverse events: 49 in the randomized phase (18 of the patients treated with tVNS and 31 patients treated with the sham device, respectively) and 42 patients in the open label phase. No serious adverse device effects (SADESs) occurred. Adverse events deemed as device related or possibly device related occurred in 35 patients during the randomized phase (11 patients amongst those treated with tVNS compared to 23 patients treated with the sham).	
75			The adverse events occurring in 25% or more of the subjects during the entire duration of the study included: Discomfort at the treatment site : 2 patients in the tVNS group and 7 patients in the sham group during the randomized phase and 4 of the patients who entered the open label phase. Skin reactions at the treatment site : none of the patients in the tVNS arm, 9 of the patients in the sham group during the randomized phase and 2 of the patients who entered the open label phase. Lip or facial dropping/pulling/twitching: 8 of the patients in the tVNS arm, none of patients in the sham group during the randomized phase and 9 of the patients, during the open label phase. Change of taste/ metallic taste: none of the tVNS treated patients, 7 of the patients in the sham group during the randomized phase and 2 of the patients in the open label phase.	

Com. no.	Consultee name and organisation	Sec. no.	Comments	Response Please respond to all comments
76			Moscato & Moscato explored the effect on Tvns for the treatment of acute migraine attacks in patients with chronic migraine (8, 9). This open label study looked at the effect of tVNS on the headache but also four other common and disabling migraine symptoms associated with the headache: nausea, vomiting, photophobia and photophobia. 22 patients treated a total of 79 attacks. In addition to attack resolution at 2 hours of half of the treated attacks an overall significant reduction of symptoms in the reminder of the attacks, was observed. Of all attacks treated less than 10% were associated with adverse events, which included transient paresthesia and muscle spasms. None of the event was serious. No patient discontinued the study due to adverse events. (8). An extension of this study further looked at the patient preference, tolerability, compliance and safety profile of the tVNS in compared to pharmacological treatments which these patients had had before. The outcome yielded supportive evidence that tVNS is well tolerated in comparison to pharmacological therapies and that tVNS has in important therapeutic potential with an advantageous safety profile (9).	

Com. no.	Consultee name and organisation	Sec. no.	Comments	Response Please respond to all comments
77			Grazzi et al (10) performed a study of tVNS for acute treatment in 30 patients with episodic migraine without aura in an open label, single arm multiple attack study. 96 migraine attacks were treated. 43 of the attacks resolved within 30 minutes. 11 of the attacks improved and did not require rescue medication. The reminder of the attacks required rescue medication at two hours. The study also contributed further favourable information to the existing safety profile. In an open label single centre six months trial, Rainero and colleagues (11) explored the potential of tVNS for the acute migraine treatment in 15 patients with chronic migraine and medication overuse headache. 362 attacks were treated with tVNS during this study . A significant response was achieved in approximately 50% of the treated patients. Pain free responses were achieved in a third of the treated attacks at 2 hours. An overall statistically significant severity reduction of the averaged attack scores was found. In addition to providing promising efficacy outcomes in a migraine population generally challenging to treat, the authors reported that all adverse events had been mild, transient and none unexpected.	

Com. no.	Consultee name and organisation	Sec. no.	Comments	Response Please respond to all comments
78			Engel at all (12) undertook detailed assessment of the cardiovascular safety profile in an open label, multicentre, single-arm, prospective study conducted between January 2012 and May 2012 looking at the safety and clinical benefits of tVNS for acute relief in patients with asthma. The study included 30 patients who treated 1 asthma attack with tVNS. Detailed cardiovascular monitoring included 12-lead electrocardiograms (ECGs) performed for 29 of the patients at 3 study visits (1 patient was excluded because only 1 ECG reading was taken at the treatment visit): ECG assessments: At Baseline At the treatment visit before tVNS application, during tVNS application, immediately after and at 5, 15, 30, 60 and 90 minutes, respectively and At the follow up visit, 7 days after the treatment. A total of 284 were obtained, looking at the heart rate, PR and the corrected QT intervals and QRS duration. The ECG findings and the impact of the tVNS treatment on those parameters were reviewed by an independent cardiologist, documented in detail, summarized and analysed. The work was presented at American Academy of Neurology in 2015. No clinically significant ECG changes were noted, either in isolated readings or in comparison to baseline. Treatment with tVNS had no meaningful effect on heart rate, PR interval, corrected QT interval or QRS duration. In addition to specific cardiac safety evidence, the overall outcomes supported the existing body of evidence that Tvns is a safe and well tolerated treatment modality.	

Com. no.	Consultee name and organisation	Sec. no.	Comments	Response Please respond to all comments
79			A detailed summary of studies using tVNS for the treatment of primary headache conditions was published by Silberstein and Yuan in the journal Headache, in October 2015 (13). The review provided further supportive evidence that tVNS has a high potential for therapeutic gain for patients with cluster headache, migraine and other primary headache disorders and a high safety profile.	

Com. no.	Consultee name and organisation	Sec. no.	Comments	Response Please respond to all comments
80			4. Silberstein S, Da Silva AN, Calhoun AH, et al. Non-invasive vagus nerve stimulation for chronic migraine prevention in a prospective, randomized, sham-controlled pilot study (the EVENT study): report from the double-blind phase [AHS abstract LBP19]. Headache. 2014;54(suppl 1):1426. 5. Silberstein S, Da Silva AN, Calhoun AH, et al. Chronic migraine prevention with non-invasive vagus nerve stimulation in a prospective pilot study (the EVENT study): report from the open-label phase [AHS abstract LBP21]. Headache. 2014;54(suppl 1):1427. 6. Tepper S, Silberstein S, Mechtler L, et al. Predefined exploratory outcomes from the study of non-invasive vagus nerve stimulation for the acute treatment (ACT1) of cluster headache [abstract LBP08; Published online September 30, 2015]. Headache. 2015. DOI: 10.1111/head.12693. 7. Silberstein S, Mechtler L, Kudrow D, et al. Efficacy and safety outcomes of the non-invasive vagus nerve stimulation for the acute treatment (ACT1) of cluster headache study [abstract LBP07; Published online September 30, 2015]. Headache. 2015. DOI: 10.1111/head.12693 8. Moscato D, Moscato FR, Liebler E. Efficacy of noninvasive vagus nerve stimulation (nVNS) in the treatment of acute migraine attacks. Headache. 2014;54(8):1418. 9.Moscato D, Moscato FR. A survey of patient perceptions of non-invasive vagus nerve stimulation (nVNS) therapy for acute migraine attacks. Cephalalgia. 2015;35(6 suppl):23.	Thank you for your comment. Conference abstracts are not normally considered adequate to support decisions on efficacy and are not generally selected for presentation in the overview, unless they contain important safety data. The Silberstein (2014) and (2015) papers are abstracts that do not report any new safety event. The Tepper (2015) paper is an abstract that does not report any new safety event. The Moscato (2014) and (2015) studies are abstracts that do not report any new safety event. The Grazzi (2014) study is an abstract that does not report any new safety event. The Rainero (2014) paper is a poster that does not report any new safety event. The Engel (2015) paper is a poster that does not report any new safety event.

Com. no.	Consultee name and organisation	Sec. no.	Comments	Response Please respond to all comments
81			10. Grazzi L, Usai S, Bussone G. Gammacore device for treatment of migraine attack: preliminary data. Neurology. 2014;82(10 suppl):I9-2.005. 11. Rainero I, De Martino P, Rubino E, Vaula G, Gentile S, Pinessi L. Non-invasive vagal nerve stimulation for the treatment of headache attacks in patients with chronic migraine and medication-overuse headache. Neurology. 2014;82(10 suppl):P1.262. 12 Engel ER, Blake J, Liebler E. Non-invasive Vagus Nerve Stimulator (gammaCore) was not associated with meaningful cardiovascular adverse effects. Neurology. 2015. 84;14:supplement P1.292 13. Yuan H, Silberstein S. Vagus Nerve Stimulation and Headache. Headache. 2015 Oct 16. doi: 10.1111/head.12721	The Yuan (2015) paper is a review on vagus nerve stimulation. It has been included in Appendix A.
82	Consultee 17 Royal College of Physicians	**General**	Dear all The RCP is grateful for the opportunity to respond to the above consultation. We would like to formally endorse the response submitted by the Association of British Neurologists (ABN). I would be grateful if you could confirm receipt. Best wishes	Thank you for your comment. .

Com. no.	Consultee name and organisation	Sec. no.	Comments	Response Please respond to all comments
83	Consultee 2 Patient	**General**	Dear Sirs I have been using Gamma core since March and can honestly say it has transformed my life . I have had migraines for twenty three years and have tried a multitude of treatments and not one has come as close as Gamma core to relieving me of this huge blight on my life . I very rarely now get a migraine ,before using Gamma core more of my time was spent suffering from or recovering from a migraine than not . Gamma core has literally given me back my life without exaggeration, I feel incredibly lucky I was allowed onto this programme and wish it were available for all who suffer . I have absolutely no side effects , which is not the case with any drug treatment available for migraines . It's immediate availability and support were fantastic , I could have not have asked for a more personal and efficient service . It would be wonderful if this were available for all with migraine . Yours faithfully	Thank you for your comment. The Committee very much welcomes hearing from patients who have undergone this procedure and considered your experience and views in their deliberations.

Com. no.	Consultee name and organisation	Sec. no.	Comments	Response Please respond to all comments
84	Consultee 3 Patient	**General**	Ref GID-IP1116 I have been using the gamma core device for approximately 18 months to treat paroxysmal hemicrania. Prior to this I had experienced excruciating headaches for 20 years. Each day I would have 15-20 episodes which would each last for 15 minutes, along with a continuos dull headache. The pain was so extreme that I would be left exhausted & I would feel constantly anxious. I had been misdiagnosed over the years with a number of conditions ranging from sinusitis to cluster headache, to migraine to dental problems to eyesight issues etc. I had been given a pharmacy full of different pills ranging from anti depressants, to morphine to epilepsy medication, a lidocaine infusion, Botox etc, none of which had eased my symptoms, & each with their own dreadful side effects. Eventually I was surviving on 20, sometimes more, nurofen plus, per day. At one point in my journey I was prescribed indomethacin but was advised that this should only be used short term. This medication had some effect on my condition, but was taken off the market shortly after, & I now have difficulty in sourcing this. Although not impossible to get, I remain on it I now have stomach & liver issues to contend with as a result of my long term use of this drug. After meeting with Professor [redacted] he suggested that I may benefit from the use of the Gamma Core device...THIS HAS CHANGED MY LIFE!!	Thank you for your comment. The Committee very much welcomes hearing from patients who have undergone this procedure and considered your experience and views in their deliberations.

Com. no.	Consultee name and organisation	Sec. no.	Comments	Response Please respond to all comments
			I use the device 3 times a day for 2.5 minutes x 3 for each session. It is easy to use & I have experienced no side effects whatsoever. I have been able to reduce the indomethacin by two thirds..& I hope that in the next few months I will be off it all together. I keep a daily headache diary & I would only experience an episode a couple of a times a month. Even these are much lower on the pain scale than before. The constant headaches & pain had such a negative effect on every aspect of my life from work to my relationship & in my social life. I couldn't plan anything, I was unable to leave the house for days, had to take numerous sick days from my job, my hobbies suffered & my partner had to have the patience of a saint! Nowadays, I wake in the morning not dreading the day ahead & my sleep has improved dramatically. Prior to using the device the headache would wake me throughout the night, but now I sleep soundly. I have been able to return to the gym, meet friends, go on holidays..all the things I couldn't do for years due to the pain that I was enduring. The gamma core device has had a tremendous positive effect on my life...it has given me my life back!	

Com. no.	Consultee name and organisation	Sec. no.	Comments	Response Please respond to all comments
85	Consultee 7 Patient organization The Migraine Trust	**General**	As a patient organisation, The Migraine Trust welcomes new devices and drugs that are proved to be safe and work. We note that many of the people who suffer from migraine find it difficult to tolerate side effects from many of the drug treatments. We know that nothing works for everybody who has this condition and we are aware anecdotally and reading the evidence that some patients find this device has helped them. We believe that the device should be prescribed through a headache clinic by a headache professional.	Thank you for your comment. The committee considered this comment but decided not to change the main recommendations.
86	Consultee 7 Patient organization The Migraine Trust	**NOTE**	The manufacturers donate small amounts of money (as do others) to support us as a patient organisation. There are no specific projects funded by them, just towards core costs as we receive no government funding.	Thank you for your comment.
87	Consultee 8 Patient	**General**	I am a migraine sufferer and I use vagus nerve treatment three times a day on a prophylaxis basis. I have benefited from an improved quality of life with severity of attacks reducing without incurring any safety issues.	Thank you for your comment. The committee very much welcomes hearing from patients who have undergone this procedure and considered your experience and views in their deliberations.

Com. no.	Consultee name and organisation	Sec. no.	Comments	Response Please respond to all comments
88	Consultee 8 Patient	**1.1**	At present my consultant (through my GMC doctor has authorised the device and this seems to be an effective and efficient process without the need for clinical governance.	Thank you for your comment. The committee very much welcomes hearing from patients who have undergone this procedure and considered your experience and views in their deliberations. The committee considered this comment but decided not to change the main recommendations.
89	Consultee 9 Patient	**General**	I would just like to feedback my experiences of GammaCore VNS which I have been fortunate to have been using since April 2015. I have suffered from migraines since I was fourteen and am now fifty one. I have suffered greatly with this condition and it has had a massive impact on both my working and personal life. During this time I have followed any new treatments with interest especially those which do not involve drug use. I jumped at the chance when offered VNS from GammaCore. It is very easy to use and convenient to carry about. Whilst it has not reduced the frequency it has greatly reduced the intensity of my migraines and I hope further use will provide even better results in the future. Following referral from [redacted] I was contacted the next day by my GammaCore Representative who arranged to meet me the following week to provide me with the device and instructions as to its use. The fact that she was able to do this so quickly was wonderful and I was therefore able to trial the device for myself and assess its effectiveness for me personally. Following this initial stage of trial I was then asked to feedback the effectiveness and obtain my doctors written consent to enable me to continue with the treatment. This ensured every stage was conducted in a patient and time friendly manner, long may it continue.	Thank you for your comment. The committee very much welcomes hearing from patients who have undergone this procedure and considered your experience and views in their deliberations.

Com. no.	Consultee name and organisation	Sec. no.	Comments	Response Please respond to all comments
90	Consultee 10 Patient	**General**	"I have used GammaCore since May 2013 under the care of Dr [redacted] at [redacted] Hospital. The device has made a huge difference to the way migraines affect my life. Before using GammaCore I was getting 14 migraines in every 28 day cycle, I'd tried every preventative the NHS recommends but had severe side effects to them all. I was offered Botox on the NHS but decided to tryGammaCore first. I use the device x3 doses at 7am and x3 doses at 3pm every day. It has reduced the number of migraines from 14 to 4 a month. The ones I do get are much milder and sometimes respond to painkillers rather than triptans. This reduction has meant I can socialise, travel abroad and engage with family and friends again. I have not had to take any time off of work since using GammaCore. The device is easy to use, I have never suffered ill effects or device failure. There is always help from the company or Dr [redacted]. As I have other medical conditions it is important to be drug free wherever possible and this is where GammaCore is fantastic. In addition I sleep better, my mood is better and overall I would not wish to be without it. The device is so simple to use, I was shown once, practised twice in front of Dr [redacted] and have never experienced pain or discomfort or side effects whatsoever. I strongly believe this device is key to getting people with migraines to be able to lead a normal life and hope it is soon available on the NHS"	Thank you for your comment. The committee very much welcomes hearing from patients who have undergone this procedure and considered your experience and views in their deliberations.

Com. no.	Consultee name and organisation	Sec. no.	Comments	Response Please respond to all comments
91	Consultee 11 Patient	**1**	"I have been using the gammaCore nVN stimulator daily, since summer 2012. It was first initiated after comprehensive training and constant follow up by the clinicians, initially at [redacted], now at at [redacted]. My concern attached to the NICE document would be, the more safety constrains you try to put in place the harder it becomes for patients, like me whom rely on this device. For example, I live in rural [redacted] and my local district general hospital does not cater for my complex neurological needs, so under the patients charter and thus ensuring streamlined and efficient, effective care I travel to a major teaching hospital. If for example, LOCAL governance approval had to be sort for the commencement of the gammaCore, this would prove problematic for patients who have complex needs. GammaCore is a novel device and the education behind it is being driven and pushed but it is change in practice and does this mean that hospitals that have governance teams less aware of the device, will be at a disadvantage?	Thank you for your comment. The committee very much welcomes hearing from patients who have undergone this procedure and considered your experience and views in their deliberations. Procedures with ‘’special arrangements for clinical governance, consent and audit or research’’ recommendation can be done in any NHS hospital providing that extra care is taken to explain the uncertainties and extra steps are put in place to record and review what happens.
92	Consultee 11 Patient	**4 and 5**	Secondly, in order to measure the success and safety of things, you need a comparator, how can this be achieved with cluster headache patients, when chronic sufferers on average can have over 8 attacks a day. I am aware that the device can reduce frequency and severity, yet, were are your end points. No doubly more and more articles about the effectiveness of the device are going to written in due course.	Thank you for your comment. The IP programme does not assess the efficacy and safety of comparator interventions. NICE may update the guidance on publication of further evidence.

Com. no.	Consultee name and organisation	Sec. no.	Comments	Response Please respond to all comments
93	Consultee 11 Patient	**General**	Long term, this device for me personally has reduced the amount of sumatriptan I use by over 90%. The cost saving to the NHS via using this per year is thousands. I can not rate or speak highly enough of the gammaCore.. I agree it probably needs to be monitored, but only by a patient register of names, not an audit of use. Clinicians are responsible for their patients and thus draw up a treatment program depend on the headaches. The gammaCore is a breakthrough is treatment that needs to be embraced and not hampered. Over the last three years, I have not had one side effect from the device and I am probably one of the longest users in the UK. "	Thank you for your comment. The committee very much welcomes hearing from patients who have undergone this procedure and considered your experience and views in their deliberations. Cost-effectiveness is not part of the remit of the IP Programme.
94	Consultee 14 Patient organisation OUCH (UK)	**6.1**	"This comment is on behalf of OUCH (UK) the support organisation for sufferers: In reading the consultation document, we note in original communication regarding this interventional procedure, you state that cluster headache is â€œquite commonâ€• . We would point out that although no definitive information is available regarding prevalence, approximately 0.05% of the UK population suffer cluster headache, whereas migraine affects 15% of the UK population , [BASH â€“ British Association for the Study of Headache, 2010.]	Thank you for your comment. Section 6.1 of the guidance has been changed and section 6.2 has been added. Please refer to response to comment 22.

Com. no.	Consultee name and organisation	Sec. no.	Comments	Response Please respond to all comments
95	Consultee 14 Patient organisation OUCH (UK)	**General**	The sufferer comments above are from a 49 year old female cluster headache sufferer and encapsulates the positive experience most users have experienced. Although we have no definitive information regarding the Gammacore device, the general overview from our members is that this is a beneficial and fast acting treatment for cluster headache attacks and OUCH strongly supports its adoption as a licensed treatment for cluster headache. This treatment is welcomed by OUCH as it is one of only two treatments which have no side effects, but is an easily accessible and portable treatment device. For cluster headache sufferers this is a big plus as it enables them to continue in employment without need for special areas to treat attacks, or to store items such as portable oxygen. It also restores their self esteem as they can abort attacks quickly and the device is much less alarming for family members and supporters to witness being used. It also benefits those who suffer other health conditions which would contra-indicate the use of the two conventional abortives for cluster headache; triptan drugs and high flow oxygen.	Thank you for your comment.
			Further, one of the licensed abortives subcutaneous sumatriptan does mean that sufferers who are needle-phobic have had little or no alternative abortive treatment and the Gammacore device would fill that gap. We look forward to seeing NICE's guidelines and further advice for the Gammacore device. Reference: MacGregor E A, Steiner T J, Davies P T G, 2010; Guidelines for all Healthcare Professionals in the Diagnosis and Management of Migraine, Tension-Type, Cluster and Medication over-sure Headache; British Association for the Study of Headache, Hull."	

Com. no.	Consultee name and organisation	Sec. no.	Comments	Response Please respond to all comments
96	Consultee 14 Patient organisation OUCH (UK) on behalf of a patient	**General**	"This comment is from a 49 year old female sufferer who uses Gammacore device to abort her cluster headache attacks: I was asked to trial the Gammacore device by Dr [redacted] at [redacted] neurology department . In the past I have tried all available treatments for my chronic cluster headaches and struggled on the maintenance dose of verapamil, due to the side effects.Â I have had the device a few months now and once shown how to use it, I found it very easy to administer the treatments. Having spent much time at appointments and taking medications, this has by far been the easiest and least problematic care plan. It also gave me the freedom to self administer treatment as and when I needed it, which felt very liberating, especially as there is no limit on the amount of times I can use it. This is a very relevant point when you have multiple attacks per day.	Thank you for your comment. The committee very much welcomes hearing from patients who have undergone this procedure and considered your experience and views in their deliberations

Com. no.	Consultee name and organisation	Sec. no.	Comments	Response Please respond to all comments
			I use the device for every acute attack and a minimum of 3 times per day as a preventative. Although I am still having regular attacks, I have found this device incredibly useful in managing my pain levels. As a mum of two young children it is much more convenient than oxygen , especially when out of the house and doesn't make me feel on edge like the injections. So I use both O2 and the Imigran injections far less now and this lessens the risk of rebound attacks. All attacks treated with the device are reduced in severity, usually by at least half. I have experienced no side effects what so ever and the more I use it the fewer attacks I seem to be getting. Sometimes, if I am having a particularly bad attack, I will use the device, oxygen and an injection . The combination can mean I will get on top of the attack and carry on with my day, previously I would be left exhausted and often the attacks would return within the hour. I am now finding the period between bad attacks has lengthened. Thankfully, I have been fortunate to have a Gammacore device over my worst period for attacks. I know that previous years I would have rarely been confident enough to have left the house. This year, so far , I have faired better and felt less anxious about leaving home, so I would be heartbroken to not have this device at my disposal. It fits easily into your bag and all my friends and family have got used seeing me use it. I truly wish I had had access to it years ago, as many of the drug therapies I tried were problematic for me and less effective in managing my illness. "	

Com. no.	Consultee name and organisation	Sec. no.	Comments	Response Please respond to all comments
97	Consultee 16 Patient	**General**	To whom it may concern, I feel compelled to write in support of the Gammacore treatment. I have chronic cluster headaches which until I was given the opportunity to take part in a gammacore trial was destroying my life. I had to give up my job and pensioned off from my professional career with intractable headaches and hemiplegic aura. I got an immediate positive response to the treatment. It has changed my life. The quality of life I have now is amazing. I am not cured but the headaches are much more controlled and the hemiplegic symptoms are much more manageable. I am now able to participate in family gatherings and make plans. I go on holidays and weekends away which I wasn't able to do previously as well as using the London Underground. (Oxygen is not permitted on the tube). Please listen to those of us who are using it. There are no side effects and only massive gains for users. Please give Gammacore the support it needs. It is a brilliant treatment that is mobile, painless with no side effects.	Thank you for your comment. The committee very much welcomes hearing from patients who have undergone this procedure and considered your experience and views in their deliberations.

Com. no.	Consultee name and organisation	Sec. no.	Comments	Response Please respond to all comments
98	Consultee 18 Patient	**General**	Dear NICE Team, I have been invited to comment on my use of TVNS which I have been in possession of for the last year.. The Gamma core device has made a huge difference to my life for the better. I am someone who suffers from a lot of headaches generally as well as clusters. Since using the device my general well being has improved as the amount of headaches and length of time I have them, has reduced considerably. The device is easy to use, transportable and has given me no side effects. When I go away from home, it goes with me. I have been told I cannot overdose with it, which is also a bonus, as medication tried in the past, has not agreed with me. The fact that this gives no side effects of chemical harm is so important when you already feel fragile and prone to unusual impacts of medication. I was sceptical that this could make a difference to me but was so relieved to find it helpful. In the autumn 2015, I only had around 6 cluster migraines when I would normally have them nightly for around 6 weeks. I am finding that I can now make tentative plans in some areas of my life, build in the confidence and knowledge of that, which I would not have been able to do before. If I can help with more specific information, please let me know. Many thanks	Thank you for your comment. The committee very much welcomes hearing from patients who have undergone this procedure and considered your experience and views in their deliberations.

Com. no.	Consultee name and organisation	Sec. no.	Comments	Response Please respond to all comments
99	Consultee 19 Patient	**General**	Dear NICE, I have been using the Gammacore device daily for a number of months. To give you some background I have suffered migraines for over 35 years that have stopped me having any kind of 'normal' life. My body seems to be very sensitive to side effects as is common with the 'migraine' brain. Since I started using gammacore my migraines have not disappeared but have lessened to a degree that I can actually plan my life. I have not suffered any 'side effects' whatsoever and have always felt well. I have been on many clinical trials before for migraine medication and have suffered various degrees of side effects but I can honestly tell you that this little machine has given me none of these. I am happy to go into more detail with a clinician if required. Kind regards	Thank you for your comment. The committee very much welcomes hearing from patients who have undergone this procedure and considered your experience and views in their deliberations.